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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,900	01/24/2006	Dominique P. Bridon	C2077-7016US	6100

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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/565,900	BRIDON ET AL.	
	Examiner	Art Unit	
	CHRISTINA BRADLEY	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,41-43,45,46,48-59,61,62,65,66,69-71,73-86,89,90,93,116-124,131 and 132* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/28/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 38,41-43,45,46,48-59,61,62,65,66,69-71,73-86,89,90,93,116-124,131 and 132.

DETAILED ACTION

Status of Claims

1. Claims 38, 41-43, 45, 46, 48-59, 61, 62, 65, 66, 69-71, 73-86, 89, 90, 93, 116-124, 131 and 132 are pending. Claims 39, 40, 44, 47, 60, 63, 64, 67, 68, 72, 87, 88, 91, 92, 94-115, and 125-130 were cancelled in the amendment filed 15 April 2009; all rejections of these claims are now moot. Claim 132 was added in the amendment filed 15 April 2009.

Specification

2. The objection to the specification regarding the use of the trademarks Lantus, Levemir, Humalog, Novolog, Apidra, Biotage, Prism, One Touch Ultra, DAC and CD is withdrawn in light of the amendment to the specification filed 15 April 2009.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 38, 41, 48, 49, 65 and 116 are under 35 U.S.C. 102(b) as being anticipated by Liu *et al.* (*Biochemistry*, **1979**, *18*, 690-7). Liu *et al.* teach *m*-maleidobenzoylinsulin (MB-insulin, p. 691, col. 2). MB-insulin was synthesized through the reaction of porcine insulin with *m*-maleidobenzoyl-*N*-hydroxysuccinimide ester (MS). The hydroxysuccinimide group reacts with free amino groups on insulin to yield insulin linked to a maleimido-containing group by a benzoyl linker (Fig. 1). Free amino acids on insulin include the N-terminal amino groups of the A and B chain and the side chain of lysine B29. Liu *et al.* does not teach that the MB-insulin can

be conjugated to blood components such as albumin or recombinant albumin. Because the structure of the insulin derivative taught by Liu *et al.* is identical to the claimed derivative, the prior of Liu *et al.* inherently meets this functional limitation. With respect to claim 116, the MB-insulin was purified in phosphate buffered saline which is a pharmaceutically acceptable carrier.

5. In the response filed 15 April 2009, Applicant traverses the rejection on the grounds that the amended claims require that the maleimido-containing reactive group be coupled only to the α- amino group of the N-terminus of the B chain of the insulin molecule, and not the α-amino group of the N-terminus of the A chain or the side chain of Lys B29, and that accordingly Liu *et al.* who do not report the protection of the α-amino group of the N-terminus of the A chain or the side chain of Lys B29 during synthesis, teach insulin derivatives with the maleimido group coupled to all three α-amino groups. This argument has been fully considered but is not persuasive. In contrast to Applicant's intent and assertion, the amended claims are not limited to insulin derivatives wherein the maleimido group is coupled to only the α-amino group of the N-terminus of the B chain. Rather, the claim is drawn to an insulin derivative **comprising** an insulin molecule and a maleimido-containing reactive group coupled to the α-amino group of the N-terminus of the B chain of the insulin molecule (emphasis added). MPEP § 2111.03 state that the transitional phrase "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. Given this interpretation of "comprising", the amended claims state that the insulin derivative must have a maleimido-containing reactive group coupled to the α-amino group of the N-terminus of the B chain but do not exclude the possibility that the insulin derivative further includes a maleimido-containing reactive group coupled to other a-amino

groups in the insulin molecule. Therefore, the MB-insulin taught by Liu *et al.* anticipates the claims and the rejection is maintained.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 38, 41-43, 45, 46, 48-59, 61, 62, 65, 66, 69-71, 73-86, 89, 90, 93, 116-124, 131 and 132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bridon *et al.* (WO 00/69900, foreign document citation No. 2 on the Information Disclosure Statement filed 01/21/2008) in view of Jones *et al.* (WO 95/05187, citation No. 6 on the Information Disclosure Statement filed 01/24/2006), Jonassen *et al.* (citation No. 9 on the Information Disclosure Statement filed 01/24/2006), Baudys *et al.* (citation No. 8 on the Information Disclosure Statement filed 01/24/2006), Bridon *et al.* (CA 2363712, citation No. 5 on the Information Disclosure Statement filed 01/24/2006) and Vajo *et al.* (*Endocrine Rev.*, **2001**, *22*, 706-717).

8. Bridon *et al.* (WO 00/69900) teach therapeutic peptides conjugated to protein carriers such as albumin (p. 3, ln29-30). Bridon *et al.* teach that maleimide derivatives of therapeutic peptides may be prepared by reacting the peptide with maleimidopropionic acid (MPA). The

MPA will react with free amines at the N-terminus or lysine side chain. (p. 73, lns. 1-14) Bridon *et al.* teaches methods of modifying peptide containing multiple cysteines with MPA at the N-terminus (example 65) and at an internal lysine (example 67). Bridon *et al.* teaches that insulin (p. 26) is an example of a therapeutic peptide that can be modified with an maleimido-containing group and subsequently conjugated to albumin.

9. Bridon *et al.* (WO 00/69900) does not explicitly recite the synthesis of the insulin derivative or conjugate.

10. Jones *et al.* teach an insulin analogue comprising insulin covalently linked to a pendant molecular group which has an affinity for one or more binding proteins present in the human or animal circulatory system to treat glycemic diseases (p. 7, lns. 1-4). The exemplified analogue comprises thyroxine conjugated to the B1 residue (pp. 15-17). Thyroxine binds non-covalently to several proteins in human circulatory system including thyroxine binding globulin, thyroxine binding prealbumin and albumin (p. 10, lns. 24-27). The insulin analogue may be injected to the blood stream where it will come into contact with the binding protein for which the pendant group has an affinity. Thus, the insulin analogue will become non-covalently bound to the blood protein and will have increased stability in the bloodstream of the patient (p. 7, lns. 5-27). Jones *et al.* differs from the instant claims in that the complex between insulin and the blood protein is non-covalent.

11. Jonassen *et al.* teach the acylation of insulin at the B29 position by fatty acids allowing binding to serum albumin (Table 1) and it use in the treatment of diabetes (p. 676).

12. Baudys *et al.* teaches an insulin conjugate comprising carboxymethyl dextan attached to the A1 position that exhibits prolonged insulin action.

13. Bridon *et al.* (CA 2363712) teach modified insulinotropic peptides conjugated to MPA at free lysines directly or via a AEEA linker, that are capable of reacting with albumin in the blood stream (p. 3, lns. 1-9).

14. Vajo *et al.* teach native human insulin (formula I) and the analogs lispro, aspart, and glargine as examples of insulins for the treatment of diabetes (abstract).

15. It would have been obvious to one of ordinary skill in the art to apply the method for the coupling of therapeutic peptides to the reactive moiety maleimidopropionic acid taught by Bridon *et al.* (WO 00/69900 and CA 2363712) to insulin and to use the resulting MPA-derivitized insulin to react with the blood protein albumin to form a stable insulin-albumin covalent complex according to the method of albumin conjugation taught by Bridon *et al.*. (WO 00/69900 and CA 2363712). The skilled artisan would have coupled the MPA to one of three free amino groups in insulin: the N-terminal alpha-amino group of the A and B chains, or the epsilon-amino group of the lysine B29 side chain based on the MPA reaction chemistry taught by Bridon *et al.* (WO 00/69900) and Bridon *et al.* (CA 2363712) and the insulin conjugation chemistry taught by Jones *et* al (B1 conjugation), Jonassen *et al.*(B29 conjugation), and Baudys *et al.* (A1 conjugation). The reactive group MPA comprises the maleimido moiety and the linker aminopriopionic acid. It would have been obvious to use any insulin such as native human insulin or the analogs taught by Vajo *et al.* It would have been obvious to make all three of the albumin conjugates described above and to test them for beneficial properties. The skilled artisan would have been motivated to do so based on the suggestion of Bridon *et al.* that insulin is a suitable peptide for the method. The skilled artisan would have been further motivated to do so based on the teachings in the prior art of Jonassen *et al.* and Baudys *et al.* demonstrating the

benefit of binding insulin to blood proteins such as albumin in order to increase stability of the molecule. There would have been a reasonable expectation of success given the conjugation chemistry taught in the references of Bridon *et al.* (WO 00/69900), Jones *et al.*, Jonassen *et al.*, Baudys *et al.* and Bridon *et al.* (CA 2363712) which show that it is possible to conjugate MPA to free amines at the N-terminus and an internal lysine of a peptide in general and that it is possible to modify the free amines of A1, B1 and lysine B29 in insulin, specifically.

16. With respect to claims 52-55 and 80-83, it would have also been obvious to use the linker AEEA-AEEA taught by Bridon *et al.* (CA 2363712). With respect to claims 116-124, it is obvious to use insulin to treat diabetes. With respect to claims 124, Bridon *et al.* (CA 2363712) teach that the conjugation method can be performed *in vivo* (p. 40, lns. 17-28). Bridon *et al.* teach that the derivatized peptide may be administered to the patient directly so that the covalent bond forms between the derivatized peptide and the blood component *in vivo*, satisfying claims 116, 118-120 and 124. With respect to claims 56-59, 62, 84-86, and 90, it would have been obvious to vary the length of the alkyl chain in MPA to optimize the linker length through routine experimentation in view of Bridon *et al.* (CA 2363712, p. 5). With respect to claims 131 and 132, Bridon *et al.* teaches that the BOC protecting group may be utilized (p. 6).

17. In the response filed 15 April 2009, Applicant traverses the rejection on the grounds that "it was not predictable that albumin covalently bound to insulin via a maleimido-containing reactive group at the N-terminal amino acid of the B chain of insulin would bind and activate the insulin receptor much less that it would exhibit significantly better binding affinity when compared to albumin covalently bound to insulin at other available positions." Applicant supports this position with data illustrating that "conjugation of albumin via a maleimido-

containing reactive group to the N-terminal amino acid of the B chain of insulin results in a significant increase in binding affinity to the insulin receptor as compared to conjugates having albumin attached via a maleimido-containing reactive group to either the N-terminal amino acid of the A chain or the lysine at position 29 of the B chain of the insulin molecule." (Table 1). Applicant's arguments have been fully considered but are not persuasive.

18. MPEP § 716.02 states that: "Any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)" In the instant case, Applicant is arguing that it is unexpected that conjugation at the N-terminal amino acid of the B chain of insulin would result in significantly better binding affinity to the insulin receptor as compared to conjugates having albumin attached via a maleimido-containing reactive group to either the N-terminal amino acid of the A chain or the lysine at position 29 of the B chain of the insulin molecule. However, a beneficial result is not necessarily an indication of non-obvious. MPEP § 716.02 states: "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967) " In order to determine if the results presented in Table I in the response filed 15 April 2009 are in fact unexpected, Applicant must support this assertion with factual evidence that the skilled artisan would have predicted a different result. Applicant does not supply such evidence in the response filed 15 April 2009. Although Applicant presents data that convincingly shows that conjugation to the α-amino group of the N-terminus of the B-

chain is superior to that at other positions in insulin, it does not present data or evidence to suggest that this result was in fact unexpected.

19. In contrast to Applicant's assertion that the superior effect of conjugating at the N-terminus of the insulin B chain was unexpected, the prior art reveals other instances wherein conjugation to this same position in insulin also resulted in superior properties. Uchio *et al.* ("Site-specific insulin conjugates with enhanced stability and extended action profile," *Advanced Drug Delivery Reviews*, **1999**, *35*, 289–306) teach the conjugation of two different hydrophilic moieties, carboxyl derivatives of monosaccharidic (Glc, Gal, Man, Fuc) glycosides and methoxypolyethylene glycols of varying MW, to the insulin GlyA1, PheB1 and/or LysB29 amino groups (seven possible derivatives). Uchio *et al.* teach that "Only site-specific modification of PheB1 amino group with either moiety resulted in pronouncedly increased resistance of insulin to fibrillation" and that "PheB1-glycosylated insulins administered subcutaneously in dogs displayed extended action profiles, the most effective being PheB1-galactosylated insulin, resembling the pharmacodynamic response of intermediate-acting insulin preparations." and that "subcutaneously administered PheB1–PEG(600)–insulin showed an even more protracted action profile..." (abstract). Hinds *et al.* ("Synthesis and Characterization of Poly(ethylene glycol)-Insulin Conjugates," *Bioconjugate Chem.* **2000,** *11,* 195-201) the conjugation of insulin to short-chain (750 and 2000 Da) methoxypoly (ethylene glycol) (mPEG) to the amino groups of either residue PheB1 or LysB29, resulting in four distinct conjugates: mPEG(750)-PheB1-insulin, mPEG(2000)-PheB1-insulin, mPEG(750)-LysB29-insulin, and mPEG(2000)-LysB29-insulin. Hind *et al.* teach that "mPEG(750 and 2000)-PheB1-insulin conjugates are substantially more stable than controls but the mPEG(750 and 2000)-LysB29-

insulin conjugates were only slightly more stable" (abstract). Given that both Uchio *et al.* and Hinds *et al.* teach that conjugation to the α-amino group of the N-terminus of the B chain of insulin more significantly impacts stability of the insulin than conjugation to other sites, it would be expected that conjugation of albumin to the α-amino group of the N-terminus of the B chain of insulin would more significantly impact stability of the insulin than conjugation of albumin to other sites. Therefore, Applicant's results in Table 1 do not constitute unexpected results even if they do convincingly illustrate that conjugation to PheB1 is superior to conjugation to GlyA1 and LysB29. The beneficial results obtained for conjugation to the PheB1 site of insulin is expected rather than unexpected in light of the prior art of Uchio *et al.* and Hinds *et al.*

20. For these reasons the rejection is maintained.

Double Patenting

21. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

22. Claims 38, 41-43, 45, 46, 48-59, 61, 62, 65, 66, 69, 71, 73-86, 89, 90, 93, 116, 117, 131 and 132 are rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claim 25 of U.S. Patent No. 7,307,148 (application No. 11/112,277 which issued as a patent since the mailing of the previous Office action). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 25 of U.S. Patent No. 7,307,148 recites insulin derivatives comprising an insulin molecule and a reactive maleimido-containing group for covalently bonding a blood protein, and conjugates of said insulin derivatives and the blood protein albumin. The species include: insulin B1-MPA, insulin B1-OA-MPA, and insulin B1-AEES2-MPA, wherein MPA is maleimidopropionic acid, OA is octanoic acid, AEES is amino ethoxy ethyl amino succinic acid and insulin is native human insulin identical to instantly claimed formula I. The albumin may be serum or recombinant (claim 6). The insulin derivatives and albumin-conjugates recited in claim 25 anticipate the instant claims.

23. Claim 42 is rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claim 25 of U.S. Patent No. 7,307,148 (application No. 11/112,277 which issued as a patent since the mailing of the previous Office action) as applied to claims 38, 41-43, 45, 46, 48-59, 61, 62, 65, 66, 69, 71, 73-86, 89, 90, 93, 116, 117, 131 and 132 above, in further view of Vajo *et al.* (*Endocrine Rev.*, **2001**, *22*, 706-717). Vajo *et al.* teach native human insulin (formula I) and the analogs lispro, aspart, and glargine as examples of insulins for the

treatment of diabetes (abstract). It would have been obvious to use any of the insulins analogs taught by Vajo *et al.* to form the insulin conjugates and derivatives claimed in copending application 11/112,277.

24. Claims 38, 41, 43, 45, 46, 48-59, 61, 62, 65, 66, 69, 71, 73-86, 89, 90, 93, 116, 117, 131 and 132 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claim 44 of copending application 11/981,474. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 44 of copending application 11/981,474 recites insulin derivatives comprising an insulin molecule and a reactive maleimido-containing group for covalently bonding a blood protein, and conjugates of said insulin derivatives and the blood protein albumin. The species recited in claim 44 of copending application 11/981,474 include: insulin B1-MPA, insulin B1-OA-MPA, and insulin B1-AEES2-MPA, wherein MPA is maleimidopropionic acid, OA is octanoic acid, AEES is amino ethoxy ethyl amino succinic acid and insulin is native human insulin identical to instantly claimed formula I. The albumin may be serum or recombinant (claim 45). The insulin derivatives and albumin-conjugates recited in claim 26 anticipate the instant claims. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

25. Claim 42 is provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claim 44 of copending application 11/981,474 as applied to claims 38, 41, 43, 45, 46, 48-59, 61, 62, 65, 66, 69, 71, 73-86, 89, 90, 93, 116, 117,

131 and 132 above, in further view of Vajo *et al.* (*Endocrine Rev.*, **2001**, *22*, 706-717). Vajo *et al.* teach native human insulin (formula I) and the analogs lispro, aspart, and glargine as examples of insulins for the treatment of diabetes (abstract). It would have been obvious to use any of the insulins analogs taught by Vajo *et al.* to form the insulin conjugates and derivatives claimed in copending application 11/981,474. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

26. Claims 38, 41-43, 45, 46, 48-59, 61, 62, 65, 66, 69, 71, 73-86, 89, 90, 93, 116, 117, 131 and 132 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 26-49 of copending application 11/982,033, in view of Bridon *et al.* (WO 00/69900, foreign document citation No. 2 on the Information Disclosure Statement filed 01/21/2008), Jones *et al.* (WO 95/05187, citation No. 6 on the Information Disclosure Statement filed 01/24/2006), Jonassen *et al.* (citation No. 9 on the Information Disclosure Statement filed 01/24/2006), Baudys *et al.* (citation No. 8 on the Information Disclosure Statement filed 01/24/2006), Bridon *et al.* (CA 2363712, citation No. 5 on the Information Disclosure Statement filed 01/24/2006) and Vajo *et al.* (*Endocrine Rev.*, **2001**, *22*, 706-717). Although the conflicting claims are not identical, they are not patentably distinct from each other.

27. Claim 27 of copending application 11/982,033 recites a modified peptide comprising a maleimido-containing reactive group coupled optionally via a linker to the peptide that is capable of covalently binding *in vivo* or *in vitro* a blood component albumin, wherein the genus of peptides includes insulin. Claim 37 of copending application 11/982,033 recites the modified

peptide conjugated to the blood component albumin, wherein the genus of peptides includes insulin. Claims 30-35 of copending application 11/982,033 recite the reactive group maleimidopropionic acid (MPA) and poly ethoxy amino acid linkers. Claim 39 recites a pharmaceutical composition comprising the modified peptide. Claims 48 and 49 recite a method of treating a disorder by administering the modified peptide or the conjugate, respectively.

28. There are no claims in copending application 11/982,033 drawn specifically to the species insulin.

29. The teachings of Bridon *et al.* (WO 00/69900), Jones *et al.*, Jonassen *et al.*, Baudys *et al.*, Bridon *et al.* (CA 2363712) and Vajo *et al.* (*Endocrine Rev.*, **2001**, *22*, 706-717) are described above.

30. It would have been obvious to select insulin from the genus of peptides recited in the claims of copending application 11/982,033and to form the MPA-modified insulin and subsequently the insulin conjugated to albumin. It would have been further obvious to use the MPA-modified insulin or the insulin-albumin conjugate to treat diabetes. The skilled artisan would have coupled the MPA to one of three free amino groups in insulin: the N-terminal alpha-amino group of the A and B chains, or the epsilon-amino group of the lysine B29 side chain based on the MPA reaction chemistry taught by Bridon *et al.* (WO 00/69900) and Bridon *et al.* (CA 2363712) and the insulin conjugation chemistry taught by Jones *et* al (B1 conjugation), Jonassen *et al.*(B29 conjugation), and Baudys *et al.* (A1 conjugation). It would have been obvious to make conjugates to all three of the reactive groups and to test them for beneficial properties. The reactive group MPA comprises the maleimido moiety and the linker

aminopriopionic acid. It would have been obvious to use any insulin such as native human insulin or the analogs taught by Vajo *et al.* The skilled artisan would have been motivated to do so based on the teachings in the prior art of Jonassen *et al.* and Baudys *et al.* demonstrating the benefit of binding insulin to blood proteins such as albumin in order to increase stability of the molecule. There would have been a reasonable expectation of success given the conjugation chemistry taught in the references of Bridon *et al.* (WO 00/69900), Jones *et al.*, Jonassen *et al.*, Baudys *et al.* and Bridon *et al.* (CA 2363712) which show that it is possible to conjugate MPA to free amines at the N-terminus and an internal lysine of a peptide in general and that it is possible to modify the free amines of A1, B1 and lysine B29 in insulin, specifically.

31. With respect to claims 52-55 and 80-83, it would have also been obvious to use the linker AEEA-AEEA taught by Bridon *et al.* (CA 2363712). With respect to claims 116-124, it is obvious to use insulin to treat diabetes. With respect to claim 124, Bridon *et al.* (CA 2363712) teach that the conjugation method can be performed *in vivo* (p. 40, lns. 17-28). Bridon *et al.* teach that the derivatized peptide may be administered to the patient directly so that the covalent bond forms between the derivatized peptide and the blood component *in vivo*, satisfying claims 116, 118-120 and 124. With respect to claims 56-59, 62, 84-86, 90, it would have been obvious to vary the length of the alkyl chain in MPA to optimize the linker length through routine experimentation in view of Bridon *et al.* (CA 2363712, p. 5). With respect to claim 131 and 132, Bridon *et al.* teaches that the BOC protecting group ay be utilized (p. 6).

32. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

33. Claims 38, 41-43, 45, 46, 48-59, 61, 62, 65, 66, 69-71, 73-86, 89, 90, 93, 116-124, 131 and 132 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-58 of copending application 11/645,297, in view of Bridon *et al.* (WO 00/69900, foreign document citation No. 2 on the Information Disclosure Statement filed 01/21/2008), Jones *et al.* (WO 95/05187, citation No. 6 on the Information Disclosure Statement filed 01/24/2006), Jonassen *et al.* (citation No. 9 on the Information Disclosure Statement filed 01/24/2006), Baudys *et al.* (citation No. 8 on the Information Disclosure Statement filed 01/24/2006), Bridon *et al.* (CA 2363712, citation No. 5 on the Information Disclosure Statement filed 01/24/2006) and Vajo *et al.* (*Endocrine Rev.*, **2001**, *22*, 706-717). Although the conflicting claims are not identical, they are not patentably distinct from each other.

34. Claim 8 of copending application 11/645,297 recites a conjugate comprising albumin covalently linked to a compound, wherein the conjugate is formed in solution by contacting albumin with a compound comprising a reactive group. Claim 34 recites the reactive group MPA. Claim 27 recites a genus of compounds including insulin.

35. There are no claims in copending application 11/645,297 drawn specifically to the species insulin.

36. The teachings of Bridon *et al.* (WO 00/69900), Jones *et al.*, Jonassen *et al.*, Baudys *et al.*, Bridon *et al.* (CA 2363712) and Vajo *et al.* (*Endocrine Rev.*, **2001**, *22*, 706-717) are described above.

37. It would have been obvious to select insulin from the genus of compounds recited in the claims of copending application 11/645,297 and to form the MPA-modified insulin and

subsequently the insulin conjugated to albumin. It would have been further obvious to use the MPA-modified insulin or the insulin-albumin conjugate to treat diabetes. The skilled artisan would have coupled the MPA to one of three free amino groups in insulin: the N-terminal alpha-amino group of the A and B chains, or the epsilon-amino group of the lysine B29 side chain based on the MPA reaction chemistry taught by Bridon *et al.* (WO 00/69900) and Bridon *et al.* (CA 2363712) and the insulin conjugation chemistry taught by Jones *et* al (B1 conjugation), Jonassen *et al.*(B29 conjugation), and Baudys *et al.* (A1 conjugation). It would have been obvious to make conjugates to all three reactive groups in insulin and to test them for beneficial properties. The reactive group MPA comprises the maleimido moiety and the linker aminopriopionic acid. It would have been obvious to use any insulin such as native human insulin or the analogs taught by Vajo *et al.* The skilled artisan would have been motivated to do so based on the teachings in the prior art of Jonassen *et al.* and Baudys *et al.* demonstrating the benefit of binding insulin to blood proteins such as albumin in order to increase stability of the molecule. There would have been a reasonable expectation of success given the conjugation chemistry taught in the references of Bridon *et al.* (WO 00/69900), Jones *et al.*, Jonassen *et al.*, Baudys *et al.* and Bridon *et al.* (CA 2363712) which show that it is possible to conjugate MPA to free amines at the N-terminus and an internal lysine of a peptide in general and that it is possible to modify the free amines of A1, B1 and lysine B29 in insulin, specifically.

38. With respect to claims 52-55 and 80-83, it would have also been obvious to use the linker AEEA-AEEA taught by Bridon *et al.* (CA 2363712). With respect to claims 116-124, it is obvious to use insulin to treat diabetes. With respect to claim 124, Bridon *et al.* (CA 2363712) teach that the conjugation method can be performed *in vivo* (p. 40, lns. 17-28). Bridon *et al.*

teach that the derivatized peptide may be administered to the patient directly so that the covalent bond forms between the derivatized peptide and the blood component *in vivo*, satisfying claims 116, 118-120 and 124. With respect to claims 56-59, 62, 84-86, 90, it would have been obvious to vary the length of the alkyl chain in MPA to optimize the linker length through routine experimentation in view of Bridon *et al.* (CA 2363712, p. 5). With respect to claims 131 and 132, Bridon *et al.* teaches that the BOC protecting group ay be utilized (p. 6).

39. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

40. Applicant did not traverse the non-statutory double patenting rejections in the response filed 15 April 2009; therefore, the rejections are maintained.

Conclusion

41. No claims are allowed.

42. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

43. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

44. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTINA BRADLEY whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 8:30 A.M. to 4:30 P.M.

45. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

46. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Christina Marchetti Bradley/
Examiner, Art Unit 1654

cmb